## REMARKS

***In the Specification:***

On page 2, please delete the paragraph beginning at line 14.

On page 2, replace the paragraph beginning at line 16 with the following:

D1 The invention also features an antibody that binds to an Api m 6 protein. The antibody can be a polyclonal or a monoclonal antibody.

***In the Claims:***

Cancel claims 37, 41, 42 and 43. Replace the pending claims with the following.

D2 28. (Thrice Amended) A method of modulating an immune response to bee venom, said method comprising administering a substantially pure bee venom polypeptide consisting essentially of the amino acid sequence of SEQ ID NO:1 to a subject in need thereof in an amount sufficient to stimulate T-cell proliferation by the subject against said bee venom.

NE 29. The method of claim 28, further comprising administering a second bee venom polypeptide to said subject.

NE 30. The method of claim 29, wherein the second bee venom polypeptide is selected from the group consisting of phospholipase $A_2$, hyaluronidase, allergen C, mellitin, adolapin, minimine, protease inhibitor, acid phosphatase, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.

NE 36. The method of claim 28, further comprising administering one or more additional bee venom polypeptides to said subject.

D3 44. (Twice Amended) A method of modulating an immune response to bee venom, said method comprising administering a composition comprising two overlapping bee venom

polypeptide fragments, wherein said overlapping fragments form the entire amino acid sequence of SEQ ID NO:1, to a subject in need thereof, in an amount sufficient to stimulate T-cell proliferation by the subject against said bee venom, wherein said overlapping fragments are between 32 and 45 amino acids in length.

D3

45. The method of claim 44, further comprising administering one or more additional bee venom polypeptides to said subject.

46. (Amended) The method of claim 45, wherein said one or more additional bee venom polypeptides are selected from the group consisting of phospholipase $A_2$, hyaluronidase, allergen C, mellitin, adolapin, minimine, protease inhibitor, acid phosphate, and glycosylated IgE-binding proteins, or analogs or derivatives thereof.

D4

47. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 3 amino acids, and wherein said polypeptide fragments are between 32 and 38 amino acids in length.

D5

48. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 5 amino acids, and wherein said polypeptide fragments are between 32 and 40 amino acids in length.

49. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 10 amino acids, and wherein said polypeptide fragments are between 32 and 45 amino acids in length.

## REMARKS

Claims 28-30, 36 and 44-49 are pending in the instant application. The amendments made herewith are fully supported by the as-filed specification. Thus, no new matter has been added.

Applicant has amended claim 28 to recite a method of modulating an immune response to bee venom by "administering a substantially pure bee venom polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 1." Applicant has also deleted the phrase "inhibit an immune response of the subject" and replaced it with "stimulate T-cell proliferation by the subject." Support for these amendments can be found, for example, at least at page 7, lines 1-7; page 8, lines 1-4; and page 10, lines 28-31.

Applicant has also amended claim 44 to recite a method of modulating an immune response to bee venom by administering a composition comprising two overlapping bee venom polypeptide fragments, wherein the fragments are between 32 and 45 amino acids in length. Support for these amendments can be found, for example, at least at the paragraph bridging pages 2 and 3; and page 11, lines 19-22.

Applicant has added new claims 47-49. Support for these claims can be found, for example, at least at page 11, lines 19-22.

There are no prior art rejections remaining in this case. There are two remaining rejections under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description. Applicant has addressed these rejections with the claim amendments made herein. Thus, these rejections should be withdrawn.

### SPECIFICATION

The Examiner has requested amendment of page two of the specification in order to provide the Accession Number for hybridoma 5E11. Applicant has elected not to make a biological deposit of this hybridoma according to the provisions of the Budapest Treaty. Therefore, Applicant has amended the corresponding paragraphs of page two of the specification accordingly.

## CLAIM REJECTIONS - § 112, FIRST PARAGRAPH

**Enablement**

The Examiner has rejected claims 28-30, 36-37 and 41-46 under 35 U.S.C. § 112, first paragraph, contending that the specification is not enabling "for *any* method of modulating an immune response wherein said method comprising administering a substantially pure polypeptide comprising (1) *any* fragment of the amino acid sequence of SEQ ID NO:1, (2) *any* fragment of between 40 and 66 amino acids in length to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide, (3) the said method further comprising administering any one or more additional bee venom polypeptides to said subject, (4) *any* method of modulating an immune response, said method comprising administering any one or more substantially pure polypeptides wherein said one or more polypeptides 'comprises' *any* 'fragments' of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof, in an amount sufficient to inhibit an immune reaction by the subject against said one or more polypeptides to said subject, (5) the said method wherein said one or more additional bee venom polypeptides are selected from the ones recited in claim 46." (Office Action at page 2.) Applicants have cancelled claims 37 and 41-43, thus this rejection, as it refers to these claims is moot and should be withdrawn.

However, the Examiner has acknowledged that the specification is enabling for a method of modulating an immune response by administering a substantially pure polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof in conjunction with a second bee venom polypeptide. (*See* Office Action at page 2.)

As noted, Applicant has amended independent claim 28 to refer to "a method of modulating an immune response to bee venom" and to replace the term "comprising" with the term "consisting essentially of." Applicant has also replaced the phrase "inhibit an immune reaction" with the phrase "stimulate T-cell proliferation." Claim 28 as amended (and, thus, dependent claims 29, 30, and 36), now recites a substantially pure bee venom polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 1 as well as a specific way of modulating an immune reaction. As acknowledged by the Examiner, the specification is

enabling for such a claim. Thus, this rejection, as it applies to amended claims 28, 29, 30 and 36, is moot and should be withdrawn.

The Examiner also contends that the specification is not enabling for claims directed to *any* fragment of the amino acid sequence of SEQ ID NO: 1. (*See* Office Action at page 2). Independent claim 44 (and, thus, dependent claims 45-49) have been amended herein to require that the overlapping polypeptide fragments form the entire sequence of SEQ ID NO:1. Claim 44 further requires that the overlapping polypeptide fragments comprise between 32 and 45 amino acids. Support for peptide fragments that are 32-45 amino acids in length (30 discrete peptide fragments) can be found, for example, at least at the paragraph bridging pages 2 and 3; and page 11, lines 19-22. Additionally, Applicant notes that the specification discloses that the peptide fragments overlap by at least 3 amino acids with at least one other peptide in the composition, *e.g.*, polypeptide fragments that overlap by between 5 and 10 amino acids, support can be found at least at the paragraph bridging pages 2 and 3; page 9, lines 18-21; and page 11, lines 19-22. If the peptide fragments that make up SEQ ID NO:1 overlap by 3 amino acids and are between 32 and 45 amino acids in length, then there are a total of 7 combinations of two overlapping fragments. If the peptide fragments that make up SEQ ID NO:1 overlap by 5 amino acids and are between 32 and 45 amino acids in length, then there are a total of 9 combinations of two overlapping fragments. Similarly, if the peptide fragments that make up SEQ ID NO: 1 overlap by 10 amino acids and are between 32 and 45 amino acids in length, then there are a total of 14 combinations of two overlapping fragments. Thus, there are a total of 30 discrete peptide fragments that make up SEQ ID NO:1, when overlapping by 3, 5, or 10 amino acids, as recited in independent claim 44, as amended herein.

The specification sufficiently enables one of ordinary skill in the art to practice the invention as now claimed, without undue experimentation. In Wands, the Federal Circuit stated,

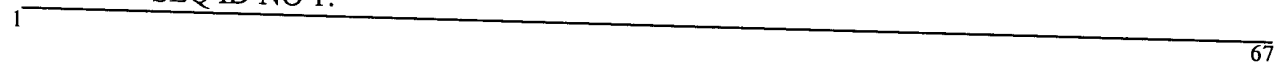
> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands, 858 F2d 731 (1988).

It is routine for one of ordinary skill in the art to make 30 peptide fragments that overlap and when combined, recite the entire amino acid sequence of SEQ ID NO:1. The table below provides evidence of these overlapping polypeptide fragments.

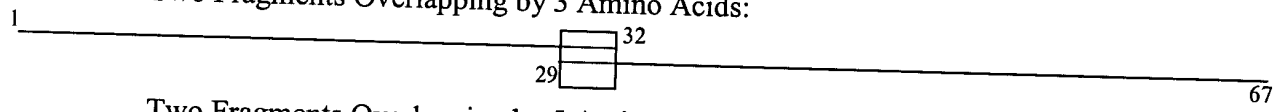
| **Overlapping by 3 Amino Acids** | | **Overlapping by 5 Amino Acids** | | **Overlapping by 10 Amino Acids** | |
|---|---|---|---|---|---|
| First Fragment | Second Fragment | First Fragment | Second Fragment | First Fragment | Second Fragment |
| 32 | 38 | 32 | 40 | 32 | 45 |
| 33 | 37 | 33 | 39 | 33 | 44 |
| 34 | 36 | 34 | 38 | 34 | 43 |
| 35 | 35 | 35 | 37 | 35 | 42 |
| 36 | 34 | 36 | 36 | 36 | 41 |
| 37 | 33 | 37 | 35 | 37 | 40 |
| 38 | 32 | 38 | 34 | 38 | 39 |
| | | 39 | 33 | 39 | 38 |
| | | 40 | 32 | 40 | 37 |
| | | | | 41 | 36 |
| | | | | 42 | 35 |
| | | | | 43 | 34 |
| | | | | 44 | 33 |
| | | | | 45 | 32 |

Information supplied in the table above is shown schematically below.

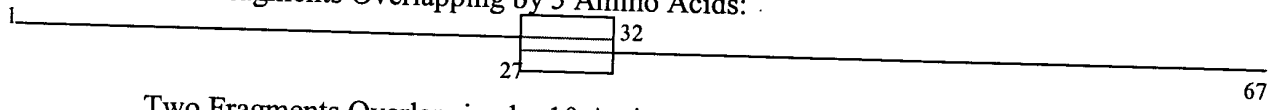
SEQ ID NO 1:



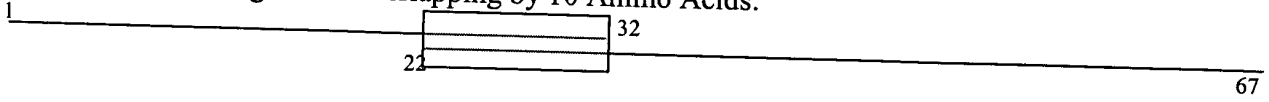

Two Fragments Overlapping by 3 Amino Acids:




Two Fragments Overlapping by 5 Amino Acids:




Two Fragments Overlapping by 10 Amino Acids:




Therefore, Applicant contends that enough information is presented in the specification to enable one skilled in the art to practice the claimed invention as amended, without undue experimentation.

Additionally, the references that the Examiner cites have nothing to do with bee venom and refer to peptides that include amino acid substitutions. Since the amended claims do not recite amino acid substitutions, Applicant contends that these references are not relevant to the invention as claimed herein.

**Written Description**

The Examiner has also rejected claims 28-30, 36-37 and 41-46 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants have cancelled claims 37 and 41-43, thus this rejection as it refers to these claims, is moot and should be withdrawn.

As noted, claim 28 (and dependent claims 29, 30, and 36) has been amended to recite a substantially pure bee venom polypeptide consisting essentially of the amino acid sequence of SEQ ID NO:1 as well as a specific way of modulating an immune reaction. Support for these amendments is found, for example, at least at page 7, lines 1-7; page 8, lines 1-4; and page 10, lines 28-31. Thus, Applicant contends that independent claim 28 (and dependent claims 29, 30, and 36), as amended herein, contains subject matter that is sufficiently described in the specification so as to reasonably convey to those skilled in the art that Applicant was in possession of the claimed invention. Accordingly, this rejection of these claims should be withdrawn.

Moreover, independent claim 44 (and dependent claims 45-49) have been amended to specify that the polypeptide fragments forming the entire sequence of SEQ ID NO:1 comprise two overlapping fragments. Claim 44 requires that the overlapping fragments contain between 32 and 45 amino acids. Support for these amendments is found at least at the paragraph bridging pages 2 and 3 and at page 11, lines 19-22.

As discussed, there are only 30 discrete peptide fragments of SEQ ID NO:1 that satisfy the requirements of claim 44. Applicant contends that one skilled in the relevant art would conclude that the specification provides a representative number of species to describe the genus of 30 discrete polypeptides. Therefore, Applicant has disclosed a sufficient number of species

within the genus and has described how to make peptide overlapping fragments between 32 and 45 amino acids long. It is not necessary to teach the skilled artisan how to make these 30 discrete polypeptides. Thus, because Applicant was in possession of the claimed genus, this rejection of these claims is improper and should be withdrawn.

## CONCLUSION

On the basis of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 20349-543.

Respectfully submitted,

Dated: December 18, 2002

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***Version with Markings to Show Changes Made***

The specification was amended by deleting the paragraph beginning at line 14 on page 2:

[The polypeptide may, in some embodiments, stimulate T-cell proliferation. Preferably, the polypeptide binds to the monoclonal antibody 5E11 (Accession No.___).].

The paragraph beginning at line 16 on page 2 was amended as follows:

The invention also features an antibody that binds to an Api m 6 protein. The antibody can be a polyclonal or a monoclonal antibody. [In some embodiments, the antibody binds to the same epitope to which the monoclonal antibody produced by the hybridoma 5E11 (Accession No._____) binds. In preferred embodiments, the antibody is the monoclonal antibody produced by the hybridoma 5E11 (Accession No. _____). The invention also includes a hybridoma producing an antibody which binds to the same epitope to which the monoclonal antibody produced by the 5E11 (Accession No. _____). Preferably, the hybridoma is the hybridoma 5E11 (Accession No. _____).].

Claim 28 was amended as follows:

28. (Twice Amended) A method of modulating an immune response <u>to bee venom</u>, said method comprising administering a substantially pure <u>bee venom</u> polypeptide [comprising] <u>consisting essentially of</u> the amino acid sequence of SEQ ID NO:1 to a subject in need thereof in an amount sufficient to [inhibit an immune reaction] <u>stimulate T-cell proliferation</u> by the subject against said [polypeptide] <u>bee venom</u>.

Claim 37 was Cancelled.

Claim 41 was Cancelled.

Claim 42 was Cancelled.

Claim 43 was Cancelled.

Claim 44 was amended as follows:

44. (Amended) A method of modulating an immune response to bee venom, said method comprising administering a composition comprising two overlapping bee venom polypeptide fragments, wherein said overlapping fragments form the entire amino acid sequence [one or more substantially pure polypeptides wherein said one or more polypeptides comprising fragments of the amino acid sequence] of SEQ ID NO:1 to a subject in need thereof, in an amount sufficient to [inhibit an immune reaction] stimulate T-cell proliferation by the subject against said bee venom, wherein said overlapping fragments are between 32 and 45 amino acids in length [one or more polypeptides, wherein the polypeptide is a fragment of between 40-66 amino acids in length].

Claims 47-49 were added:

--47. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 3 amino acids, and wherein said polypeptide fragments are between 32 and 38 amino acids in length.

48. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 5 amino acids, and wherein said polypeptide fragments are between 32 and 40 amino
acids in length.

49. (New) The method of claim 44, wherein said two overlapping bee venom polypeptide fragments overlap by 10 amino acids, and wherein said polypeptide fragments are between 32 and 45 amino acids in length.--